CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

The CIRM Medical and Ethical Standards Regulations

The following CIRM Medical & Ethical Standards regulations became effective November 22, 2006, and apply to all CIRM-funded research. An electronic version of this document is also available at www.cirm.ca.gov.

§ 100010. Scope of Chapter 2 – Stem Cell Research.

The standards set forth in this chapter apply to all institutions, as defined by Title 17, California Code of Regulations, section 100020, subdivision (f), performing research, as defined in Title 17, California Code of Regulations, section 100020, subdivision (d), funded by the California Institute for Regenerative Medicine (CIRM) as authorized by Article XXXV of the California Constitution.

§ 100020. Definitions.

As used in this chapter:

(a) "Acceptably derived" means derived in accordance with the requirements of Code of California Regulations, Title 17, sections 100080 and 100090.

(b) "CIRM" means the California Institute for Regenerative Medicine.

(c) "Covered stem cell line" means a culture-derived, human pluripotent stem cell population that is capable of: (1) sustained propagation in culture; and (2) self-renewal to produce daughter cells with equivalent developmental potential. This definition includes both embryonic and non-embryonic human stem cell lines regardless of the tissue of origin. "Pluripotent" means capable of differentiation into mesoderm, ectoderm, and endoderm.

(d) "Funded research" means research supported in whole or part by funds authorized by article XXXV of the California Constitution. For the purpose of this chapter, training activities supported by such funds shall be considered funded research.

(e) "Human subject" means a living individual about whom an investigator (whether professional or student) conducting research obtains:
(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information.

(f) "Institution" means any public or private entity or agency (including federal, state, local or other agencies).

(g) "Institutional Review Board" ("IRB") is an entity established in accordance with Title 45, Code of Federal Regulations, section 46.107, revised June 23, 2005.

(h) "Permissible Expenses" means necessary and reasonable costs directly incurred as a result of donation or participation in research activities. Permissible expenses may include but are not limited to costs associated with travel, housing, child care, medical care, health insurance and actual lost wages.

(i) "Research" means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of these regulations, whether or not they are conducted or supported under a program which is considered research for other purposes.

(j) "Somatic Cell Nuclear Transfer" ("SCNT") means the transfer of a somatic cell nucleus into an oocyte.

(k) "Stem Cell Research Oversight Committee" ("SCRO" committee) means a committee established in accordance with Code of California Regulations, Title 17, section 100060.

§ 100030. Activities Not Eligible for CIRM Funding.

The following activities are not eligible for CIRM funding:

(a) Human reproductive cloning, as defined in California Health and Safety Code Section 125292.10. subdivision (k), or reproductive uses of SCNT prohibited by article XXXV, section 3, of the California Constitution.

(b) The culture in vitro of (i) any intact human embryo or (ii) any product of SCNT, parthenogenesis or androgenesis, after

the appearance of the primitive streak or after 12 days whichever is earlier. The 12 day prohibition does not count any time during which the embryos and/or cells have been stored frozen.

(c) The introduction of stem cells from a covered stem cell line into nonhuman primate embryos.

(d) The introduction of any stem cells, whether human or nonhuman, into human embryos.

(e) Breeding any animal into which stem cells from a covered stem cell line have been introduced.

(f) The transfer to a uterus of a genetically modified human embryo.

§ 100040. Institutional Assurance of Compliance.

(a) All research institutions shall be responsible for providing written assurance satisfactory to CIRM that CIRM-funded research complies with the requirements set forth in this chapter.

(b) Each institution shall:

(1) Ensure that the chancellor, chief executive officer or person with plenary authority designates an institutional official responsible for oversight of and documentation of compliance for CIRM-funded research;

(2) Designate one or more SCRO committee(s) established in accordance with the requirements of Code of California Regulations, title 17, section 100060;

(3) Designate one or more IRB(s);

(4) Ensure that clinical personnel who have a conscientious objection not be required to participate in providing donor information or securing donor consent for research use of gametes or embryos. That privilege shall not extend to the care of a donor or recipient.

§ 100050. Compliance.

Grantees must report promptly to CIRM any failure to comply with the terms and conditions of an award. Depending on the severity and duration of the non-compliance, CIRM actions may include, but are not limited to, the following:

(a) Temporary withholding of payment;

(b) Placing special conditions on awards;

(c) Conversion to a reimbursement payment method;

(d) Precluding the grantee (principal investigator (PI) or grantee organization, as appropriate) from obtaining future awards for a specified period;

(e) Debarment from receipt of further CIRM funds;

(f) Recovery of previously awarded funds;

(g) Civil action, including referring the matter to the Office of the Attorney General of the State of California for investigation and enforcement;

(h) Other available legal remedies.

§ 100060. SCRO Committee Membership and Function.

(a) A SCRO committee shall be comprised of persons with expertise in, including but not limited to, developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical issues in stem cell research. A SCRO committee shall include at least one non-scientist member of the public who is not employed by, or appointed to, or remunerated by the relevant research institution and who is not part of the immediate family of a person who is affiliated with the institution. In addition, a SCRO committee shall include at least one patient advocate.

(b) Any member of a SCRO committee may be reimbursed for reasonable out-of-pocket expenses for attending the meeting, not including lost wages. No SCRO committee may have a member participate in the SCRO committee's initial or continuing review of any project in which the member has a conflicting interest, except to provide information to the SCRO committee.

(c) The designated SCRO committee shall provide scientific and ethical review of CIRM-funded research consistent with the requirements of Section 100070 and other applicable CIRM requirements.

(d) The SCRO committee shall facilitate education of investigators with applicable requirements of this chapter.

(e) A SCRO committee may provide oversight for two or more funded research institutions, provided the SCRO committee has oversight authority consistent with the requirements of this chapter.

(f) A SCRO committee may be convened by an institution, a group of institutions, the CIRM or other state agency.

§ 100070. SCRO Committee Review and Notification.

(a) CIRM-funded research involving the procurement or use of human oocytes may not commence without SCRO committee review and approval in writing. For such SCRO committee review and approval, a member of the committee with expertise in assisted reproduction shall be present. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (a)(3) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to use oocytes including a justification for the number needed. If SCNT is proposed a justification for SCNT shall be provided.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Animal Care and Use Committee (IACUC), Institutional Bioethics Committee (IBC), or other mandated review.

(b) CIRM-funded research involving use of human embryos may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (b)(3) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to use embryos including a justification for the number needed.

(2) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(3) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Animal Care and Use Committee (IACUC), Institutional Bioethics Committee (IBC), or other mandated review.

(c) CIRM-funded research with the aim to derive or create a covered stem cell line may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (c)(4) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for the need to derive a covered stem cell line.

(2) If SCNT is proposed as a route to generating human stem cell lines, a justification for SCNT shall be provided.

(3) Demonstrate experience, expertise or training in derivation or culture of human or nonhuman stem cell lines.

(4) Provide documentation of compliance with any required review of the proposed research by an IRB, Institutional Bioethics Committee (IBC), or other mandated review.

(5) Document how stem cell lines will be characterized, validated, stored, and distributed to ensure that the confidentiality of the donor(s) is protected.

(d) CIRM-funded purely in vitro research utilizing covered stem cell lines may not commence without written notification to the designated SCRO committee. At a minimum, the notification shall:

(1) Provide assurance that all covered stem cell lines have been acceptably derived.

(2) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(e) CIRM-funded research introducing covered stem cell lines into non-human animals or introducing neural-progenitor cells into the brain of non-human animals at any state of embryonic, fetal, or postnatal development may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (e)(3) of this regulation as a condition of granting its approval. The SCRO committee may establish guidelines and procedures for expedited review of animal research so that review by the entire SCRO committee is not required. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific rationale for introducing stem cells into non-human animals.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

(4) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(f) CIRM-funded research introducing stem cells from covered stem cell lines into a live born human may not commence without SCRO committee review and approval in writing. The designated SCRO committee may require that modification be made to proposed research or documentation of compliance with the requirements of subdivision (f)(4) of this regulation as a condition of granting its approval. At a minimum, the SCRO committee shall require the investigator to:

(1) Provide an acceptable scientific for rationale introducing stem cells into humans.

(2) Provide assurance that all covered stem cell lines have been acceptably derived.

(3) Evaluate the probable pattern and effects of differentiation and integration of the human cells into the human tissues.

(4) Provide documentation of compliance with any required review of the proposed research by an IRB, IACUC, IBC, or other mandated review.

(g) In cases where SCRO committee approval is required, a SCRO committee shall notify investigators in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure SCRO committee approval of the research activity. If the SCRO committee decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(h) SCRO committee approvals shall be reviewed no less frequently than once per year. The renewal review shall confirm compliance with all applicable rules and regulations. The SCRO committee may establish guidelines and procedures for expedited review of renewals so that review by the entire SCRO committee is not required.

§ 100080. Acceptable Research Materials.

All covered stem cell lines used in CIRM-funded research must be “acceptably derived.” To be “acceptably derived,” the stem cell line must:

(a) Have been approved by the National Institutes of Health, or

(b) Been deposited in the United Kingdom Stem Cell Bank, or

(c) Been derived by, or approved for use by, a licensee of the United Kingdom Human Fertilization and Embryology Authority, or

(d) Been derived in accordance with the Canadian Institutes of Health Research Guidelines for Human Pluripotent Stem Cell Research under an application approved by the National Stem Cell Oversight Committee, or

(e) Have been derived under the following conditions:

(1) Donors of gametes, embryos, somatic cells or human tissue gave voluntary and informed consent.

(2) Donors of gametes, embryos, somatic cells or human tissue did not receive valuable consideration. This provision does not prohibit reimbursement for permissible expenses as determined by an IRB;
(3) A person may not knowingly, for valuable consideration, purchase or sell gametes, embryos, somatic cells, or human tissue for research purposes pursuant to this chapter. This provision does not prohibit reimbursement for permissible expenditures as approved by a SCRO committee or IRB, or permissible expenses as determined by an IRB. "Permissible expenditures" means necessary and reasonable costs directly incurred as a result of persons, not including human subjects or donors, providing gametes, embryos, somatic cells, or human tissue for research purposes. Permissible expenditures may include but are not limited to costs associated with processing, quality control, storage, or transportation of materials.
(4) Donation of gametes, embryos, somatic cells or human tissue was overseen by an IRB (or, in the case of foreign sources, an IRB-equivalent);
(5) Individuals who consented to donate stored gametes, embryos, somatic cells or human tissue were not reimbursed for the cost of storage prior to the decision to donate.

§ 100090. Additional Requirements for CIRM-Funded Derivation.

Where CIRM funds are to be used to derive new human stem cell lines, in addition to the requirements of Code of California Regulations, title 17, section 100080, subdivision (e), the SCRO committee must confirm that donors of gametes, embryos, somatic cells or human tissue have given voluntary and informed consent in accordance with Code of California Regulations, title 17, section 100100.

§ 100095. Additional Requirements for CIRM-Funded Research Involving Oocytes.

When procurement of oocytes are required for CIRM-funded research, the SCRO committee must confirm the following conditions have been met:
(a) The clinic performing oocyte retrieval is a member of the Society for Assisted Reproductive Technology.
(b) The procurement and disposition for research purposes of oocytes initially provided for reproductive uses, either for use by the donor or another woman, shall not knowingly compromise the optimal reproductive success of the woman in infertility treatment. Pursuant to this requirement, the SCRO shall confirm the following:
(1) The infertility treatment protocol is established prior to requesting or obtaining consent for a donation for research purposes and that the prospect of donation for research does not alter the timing, method, or procedures selected for clinical care.
(2) The woman in infertility treatment makes the determination that she does not want or need the oocytes for her own reproductive success.
(3) The donation of oocytes for research is done without valuable consideration either directly or indirectly.
(4) If the procurement of oocytes involves a donor providing oocytes for another woman's reproductive use, then the donation to research must be expressly permitted by the original donor.
(5) If the procurement of oocytes involves use of materials donated for reproductive use by another woman and with valuable consideration in excess of reimbursement for permissible expenses for the oocyte donor, then oocytes may not be used for CIRM-funded research.
(c) The CIRM-funded institution shall develop procedures to ensure that an individual who donates oocytes for CIRM-funded research has access to medical care that is required as a direct and proximate result of that donation. Such care shall be provided at no cost to the donor. If a donor is medically insured, the donor shall not be

required to claim any treatment costs through her own insurance policy.

(d) The physician attending to any donor and the principal investigator shall not be the same person unless exceptional circumstances exist and an IRB has approved an exemption from this requirement.

(e) The physician performing oocyte retrieval shall not have a financial interest in the outcome of the research.

§ 100100. Informed Consent Requirements.

(a) All CIRM-funded human subjects research shall be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005, and California Health and Safety Code section 24173. In accordance with existing law, California Health and Safety Code section 24173 does not apply to a person who is conducting research as an investigator within an institution that holds an assurance with the United States Department of Health and Human Services pursuant to Title 45 Code of Federal Regulations Part 46, revised June 23, 2005, and who obtains informed consent in the method and manner required by those regulations.

(b) In addition to the requirements of Code of California Regulations, title 17, section 100080, the following provisions apply when CIRM funded research involves donation of gametes, embryos, somatic cells or human tissue or derivation of new covered stem cell lines which donation or derivation occurs after the effective date of this Chapter:

(1) CIRM-funds may not be used for research that violates the documented preferences of donors with regard to the use of their donated materials. The SCRO committee or IRB must confirm that donors of gametes, embryos, somatic cells or human tissue to be used to derive stem cell lines have given voluntary and informed consent in accordance with this section. To ensure donors are fully informed of the potential uses of donated materials, researchers shall disclose, in addition to the general requirements for obtaining informed consent identified in subdivision (a) of this regulation, all of the following, unless a specific item has been determined by the SCRO committee or IRB to be inapplicable:

(A) Derived cells or cell products may be kept for many years.

(B) Whether the identity(ies) of the donor(s) will be ascertainable to those who work with the resulting cells or cell products. If the identity(ies) of the donor(s) are retained (even coded), CIRM-funded researchers must discuss any plans for recontact of donors of materials used to derive cell lines and obtain consent for recontact. This requirement includes both recontacting donors to provide information about research findings and to ask for additional health information. Recontact may only occur if the donor consents at the time of donation.

(C) Researchers may use cell lines for future studies, some of which may not be predictable at this time.

(D) Derived cells or cell products may be used in research involving genetic manipulation.

(E) Derived cells or cell products may be transplanted into humans or animals.

(F) Derived cells or cell products are not intended to provide direct medical benefit to the donor(s), except in the case of autologous donation.

(G) The donation is being made without restriction regarding who may be the recipient of transplanted cells, except in the case of autologous donations.

(H) That neither consenting nor refusing to donate materials for research will affect the

quality of any future care provided to potential donors.

(I) That the results of research may be patentable or have commercial potential, and that the donor will not receive patent rights and will not receive financial or any other benefits from future commercial development.

(2) Researchers shall offer donors an opportunity to document their preferences regarding future uses of their donated materials. Researchers may choose to use materials only from donors who agree to all future uses.

(3) For CIRM-funded research involving the donation of oocytes, the IRB finding that risks are reasonable even if there is no anticipated benefit to the donor shall be documented and made available to the donor, SCRO and the CIRM. In addition, the following requirements apply:

(A) The description of foreseeable risk required in subdivision (a) of this regulation shall include but not be limited to information regarding the risks of ovarian hyperstimulation syndrome, bleeding, infection, anesthesia and pregnancy.

(B) The physician must disclose his or her relationship to the research or researcher(s) to the egg donor.

(C) Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the donor shall be informed of their right to determine the method of recontact. The donor must be informed that they have the option to initiate recontact. The investigators shall not initiate recontact unless the donor has consented, and this consent is documented in the research record.

(D) The researcher shall ascertain that the donor has understood the essential aspects of the research, following a process approved by the designated IRB or SCRO committee. Understanding the essential aspects of the research includes understanding at least that:

(i) Their eggs will not be used for reproductive purposes.

(ii) There are medical risks in oocyte donation, including the risks of ovarian hyperstimulation syndrome, bleeding, infection, anesthesia, and pregnancy.

(iii) The research is not intended to benefit them or any other individuals directly at this time.

(iv) Whether stem cell lines will be derived from their oocytes through fertilization, SCNT, parthenogenesis, or some other method.

(v) Stem cell lines developed from their oocytes will be grown in the lab and shared with other researchers for studies in the future.

(vi) If stem cells are to be transplanted into patients, researchers might recontact the donor to get additional health information.

(vii) Donors receive no payment beyond reimbursement for permissible expenses.

(viii) Stem cell lines derived as a result of their oocyte donation may be patented or commercialized, but donors will not share in patent rights or in any revenue or profit from the patents.

(4) For CIRM-funded research involving the donation and destruction of embryos for stem cell research, the informed consent process shall include a statement that embryos will be destroyed in the process of deriving embryonic stem cells.

(5) For CIRM-funded research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.

(6) For CIRM-funded research involving the donation of somatic cells for SCNT, informed consent shall include a statement as to whether the donated cells may be available for autologous treatment in the future.

§ 100110. Fairness and Diversity in Research.

CIRM grantees shall comply with the California Health Research Fairness Act, California Health and Safety Code, sections 439.900-439.906, and Inclusion of Women and Minorities in Clinical Research Act, Health and Safety Code, sections 100237-100239.

This document contains the final Medical and Ethical Standards regulations. Additional regulations may be applicable to CIRM funded research.

See: http://www.cirm.ca.gov/laws/default.asp

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